Exhibit A

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Docket Number:	UW Vaezy et al.

11/00V

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Small Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

jc542 U.S. PTO 60/100812 09/18/98

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TITLE OF THE INVENTION (280 characters max)

APPLICATIONS OF HIGH INTENSITY FOCUSED ULTRASOUND IN OBSTETRICS AND GYNECOLOGY

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 6 — ☒ Small Entity Statement

☒ Drawing(s) — *Number of Sheets* 8 — ☐ Other (specify) [ ]

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

		FILING FEE AMOUNT
☒ A check or money order is enclosed to cover the filing fees		$75.00
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☐ Yes, the name of the U S. Government agency and the Government contract number are: _____

_____

Respectfully submitted,

SIGNATURE Delbert J Barnard Date 09/18/1998

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231

P19SMALL/REV04

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Small Entity)

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Certificate of Mailing by Express Mail No. EE866829611US

I certify that this provisional patent application cover sheet, provisional patent application and fee is being deposited on 9/18/98 with the U.S. Postal Service as "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

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VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27 (d)) - NONPROFIT ORGANIZATION	Docket No. UW-Vaezy

Serial No.	Filing Date	Patent No.	Issue Date

Applicant/
Patentee: **Vaezy et al.**

Invention:

APPLICATIONS OF HIGH INTENSITY FOCUSED ULTRASOUND IN OBSTETRICS AND GYNECOLOGY

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION: **University of Washington**
ADDRESS OF ORGANIZATION: **1107 N.E. 45th, Suite 200**
Seattle, WA 98105

TYPE OF NONPROFIT ORGANIZATION:

- ☒ University or other Institute of Higher Education
- ☐ Tax Exempt under Internal Revenue Service Code (26 U.S.C. 501(a) and 501(c)(3))
- ☐ Nonprofit Scientific or Educational under Statute of State of The United States of America
  Name of State: Citation of Statute:
- ☐ Would Qualify as Tax Exempt under Internal Revenue Service Code (26 U.S.C. 501(a) and 501(c)(3)) if Located in The United States of America
- ☐ Would Qualify as Nonprofit Scientific or Educational under Statute of State of The United States of America if Located in The United States of America
  Name of State: Citation of Statute:

I hereby declare that the above-identified nonprofit organization qualifies as a nonprofit organization as defined in 37 C.F.R. 1.9(e) for purposes of paying reduced fees to the United States Patent and Trademark Office regarding the invention described in:

- ☒ the specification to be filed herewith.
- ☐ the application identified above.
- ☐ the patent identified above.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the above-identified nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed on the next page and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

☐ no such person, concern or organization exists.
☒ each such person, concern or organization is listed below.

FULL NAME University of Washington
ADDRESS 1107 N.E. 45th, Suite 200, Seattle, WA 98105

☐ Individual ☐ Small Business Concern ☒ Nonprofit Organization

FULL NAME
ADDRESS

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME
ADDRESS

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME
ADDRESS

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: David Brown
TITLE IN ORGANIZATION: Technology Manager
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SIGNATURE: David R. Brown DATE: Sept. 18, 1998

Summary of the Invention

The invention utilizes high intensity focused ultrasound (HIFU) for treatment of clinical problems in obstetrics and gynecology. In this disclosure, 13 specific problems and their current clinical management are listed. A search of the medical databases revealed no previous work on the use of HIFU for the treatment of these problems. We believe that HIFU may provide a superior management of these problems due to its capabilities of 1) penetrating the tissue without significantly affecting the intervening tissue, 2) cauterizing the tissue during the treatment to prevent/arrest bleeding, and 3) causing a mechanical effect (cavitation) in the tissue.

Four different methods of HIFU application can be envisioned, transvaginal, transrectal, transabdominal, and laparoscopic. Appropriate HIFU probes for each method of application, and concomitant imaging/mapping techniques for guidance of therapy are required and will be investigated in the future. Optimal HIFU parameters including frequency, power, duration, and mode (continuous wave or pulsed), will also be investigated in the future.

Background

This project involves research and development of a method of treatment for uterine fibroids, using High Intensity Focused Ultrasound (HIFU). Uterine fibroids, which are benign tumors of the uterus, develop in more than half of all women, and are the most common indication for major surgery in women, accounting for about 30% of all hysterectomies. The current treatment methods, whether medical (using drugs) or surgical, suffer from significant drawbacks. The tumor recurrence rate is 100% after drug therapy is stopped, and 15% after surgical removal of the tumor. Significant risks such as blood loss, intra-abdominal infection, and damage to vital organs are associated with the surgical procedure of removing the tumor(s) or the whole uterus. The cost of treatment is approximately $1,200 for a 3-month regimen of drug therapy, and $5000-$14000 for an operation. A cost of $1.2 billion to $3.6 billion is estimated for the 260,000 uterine fibroid procedures per year in the United States.

Uterine fibroids, also known as leiomyomas, are benign tumors of the uterus, occurring predominantly in the fifth decade of a woman's life. Uterine fibroids may be single but most often are multiple within the myometrium (the muscular wall of the uterus). The fibroids are actually not fibrous, but consist of muscle, probably arising from uterine smooth muscle cells, but possibly from connective tissue or the smooth muscle cells of uterine arteries (Christiansen 1993). They vary in size from 1 cm to 15 cm. They can rarely spontaneously necrose when they outgrow their blood supply. They are considered to be estrogen-dependent tumors and, perhaps because of this, are associated with a four-fold increase in the risk of endometrial carcinoma (cancer of the mucous lining of the uterus).

Fibroids are classified according to their location, as submucosal, intramural, subserosal, or pedunculated. They could also become intraligamentous (Christiansen 1993).

While most of the fibroids (50%-80%) are asymptomatic, when the symptoms do occur, they include excessive bleeding, pelvic pain, symptoms related to pressure on adjacent organs (back pain and urinary problems), anemia, and silent ureteral obstruction (Carlson et al. 1993). Fibroids are also associated with an increased incidence of infertility, and are thought to be responsible for 2%-10% of infertility cases (Christiansen 1993).

Diagnosis of uterine fibroids is performed by pelvic examination, ultrasound, MR imaging, CT scan, and endoscopy (Hutchins 1995). Ultrasound has proven to be the most useful diagnostic tool (Hutchins 1995), and MR, while highly accurate in depicting the number, size and location of fibroids, is costly and does not provide significant diagnostic information beyond that of ultrasound (Christiansen 1993).

Drug therapy may shrink, but cannot eliminate fibroids, and once therapy is stopped, the fibroids usually grow back. Drug therapy has side effects such as hot flashes, weight gain, nausea, headaches, mood changes, bloating, and decreased cognition. It is expensive, typically costing about $1,200 for a 3-month treatment regimen. Myomectomy, the surgical removal of the fibroid, is frequently preformed, but has associated risks, including fatal blood chemistry abnormalities, uterine perforation, and complications caused by stray electrical currents. Myomectomies require laparotomy, and require a prolonged hospital stay. There is a 15% rate of recurrence of the fibroid after myomectomy. Hysterectomy, the surgical removal of the whole uterus, is the second most-frequently performed female surgical procedure, only exceeded by Cesarean section. An estimated 1.5 million hysterectomies are performed annually, worldwide, with an in indication of uterine fibroid accounting for 30% of them. Complications of hysterectomies as a treatment for fibroids include intra-abdominal infection, wound infection, hemorrhage and damage to vital organs. Extensive blood loss, requiring transfusion, may accompany any type of surgery involving uterine fibroids. Both myomectomy and hysterectomy are expensive, typically costing $5000-$14000. This is a cost of $1.2 billion to $3.6 billion for the 260,000 uterine fibroid procedures per year in the United States.

Invention

The preferred embodiment is an integration of a commercially-available ultrasound imaging scanner with a HIFU transducer. The imaging and treatment transducers is aligned so that the focal spot of the HIFU transducer, where necrosis of tissue takes place is visualized on the ultrasound image. Both the targeting of the tumor region and monitoring of the HIFU treatment are performed using ultrasound image guidance and characterization.

We have performed a pilot study, "treatment of uterine fibroid models using HIFU". The pilot study was designed to provide preliminary results on the effects of HIFU on a uterine fibroid animal model, nude mice bearing sub-cutaneous tumors, grown from a rat uterine fibroid cell line (Howe et al. 1997). To our knowledge, this model is one of the

two animal models for uterine fibroids. The other model is the rat model from which the cell line is established. We have cultured the benign cell line, and have established the uterine fibroid model in nude mice in our facility. Tumor growth is induced by a single injection of approximately $5x10^6$ cells, sub-cutaneously in the suprascapular region. Tumors become visible after about 1-2 weeks.

In our pilot study, HIFU was applied to tumors, with volumes in the range of 0.2-1 ml, as measured by calipers. The treatment protocol consisted of making an incision in the skin of the animal over the tumor, to expose the tumor. Care was taken to preserve the vascular supply of the tumor during mechanical manipulation. HIFU was applied using a 3.5 MHz transducer, equipped with a conical coupler that was filled with sterilized saline. The water in the cone provided acoustic coupling to the tumor. The HIFU intensity was approximately 2000 W/cm^2. See Figure 1.

The results show that HIFU provides an effective treatment of uterine fibroid model in nude mice. The tumor volume was decreased by 70%-100% after the HIFU treatment within 7-21 days. A complete successful treatment (100% decrease: complete tumor shrinkage) was observed in 2 animals. The tumor volume before the treatment may be an important factor in the outcome of the treatment, as tumors that completely shrunk, were approximately 0.2 ml.

Figure 2 shows the average change in the tumor volume after treatment. While the SHAM treated tumors continued to grow to approximately twice their size at the time of the treatment, the HIFU-treated tumors shrunk to an average of approximately 38% of their size at the time of the treatment, within 1-3 weeks. If we don't consider the animals that did not respond to treatment at all (animals #3 and 4), the rate of shrinkage was about 87%.

Ultrasound images of the tumors were obtained before and after treatment (HIFU or SHAM). An intra-operative ultrasound imaging probe (ATL, CL10-5) was used for imaging. The results show that ultrasound imaging can be used for visualization of tumors, as well as monitoring the treatment. See Figure 3. The tumors, before the treatment, appeared as hypoechoic (dark) regions in the image. After the treatment with HIFU focal hyperechoic (bright) regions were observed in the tumor. These hyperechoic regions may represent HIFU lesion regions. The SHAM-treated tumor did not exhibit hyperechoic regions.

Histologcial analysis of the tumors has also been performed. A tumor was excised, fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin. The entire tumor, examined by light microscopy contained patchy areas of necrosis (approximately 50% of the areas examined). The necrosed areas appeared as dark-pink stained regions. Sharp demarcation existed between the necrosed and normal tumor regions. Higher magnification micrographs provided evidence of nuclear fragmentation in the necrosed areas.

Based on the results of the pilot study, a HIFU probe embodiment is considered. The HIFU probe consists of an imaging transducer array, and a HIFU transducer. The two

component of the system are integrated to for simultaneous imaging and therapy. See Figure 5.

At the time of insertion of the probe into the vaginal canal, the HIFU transducer is in the upright position. The HIFU transducer is tilted to allow targeting of a fibroid at a particular location on the ultrasound imaging plane. See Figure 6. The imaging probe is operated by the corresponding imaging machine which allows signal processing, scan conversion, color flow, Doppler and M-mode to be performed by software. Such technology allows an easy integration of the imaging and the HIFU probe. This integration is be possible by special triggering of the imaging unit, while HIFU is off. An embodiment includes a duty cycle of 50% for HIFU, and a duty cycle of 50% for the imaging unit. In this manner, ultrasound monitoring of the HIFU treatment area is possible.

Broadening

Other embodiments of the invention include: (1) HIFU frequencies in the range of 1-10 MHz; (2) Pulsed HIFU application; (3) transrectal approach; (4) any combination of the above.

The HIFU probe can be applicable to a variety of problems in obstetrics and gynecology including the following:

1. Uterine Fibroids, also known as Leiomyomas. A benign tumor of muscle cell origin found in any tissue that contains smooth muscle such as the uterus. Fibroids are the most frequent pelvic tumors, with the highest incidence occurring during the fifth decade of a woman's life. Uterine fibroids may be single but most often are multiple within the myometrium of the uterus. Fibroids are uncovered in 25% of caucasian women and 50% of african-american women. They vary in size from 1 cm to 15 cm. They can rarely spontaneously necrose when they outgrow their blood supply. They are considered to be estrogen-dependent tumors. Management is usually hysterectomy or myomectomy.

2. Endometrial Polyps: A localized outgrowth of the endometrial glands and stroma projecting beyond the surface of the endometrium and including a vascular stalk. There may be single or multiple polyps in a woman's uterus. Polyps occur in all age groups with a peak incidence between the ages of 40 and 49. Symptoms associated with polyps include abnormal bleeding patterns. Malignant transformation in an endometrial polyp is rare. Management is usually surgical dilatation and curettage.

3. Follicular Cysts: By far the most frequent cystic structures seen in normal ovaries. Also, seen in abundance in polycystic ovary syndrome. The average size of a follicular cyst is 2 cm. They are not neoplastic but can cause symptoms if enlarged. When they rupture, they can cause intraperitoneal bleeding. Oral contraceptive agents are usually the first line of defense to prevent large cysts from forming.

4. PolyCystic Ovarian Syndrome (PCOS): This condition and its severe form, stromal hyperthecosis, are marked by multiple follicuar cysts. Adhesion formation is a serious complication of surgical treatment (ovarian drilling), resulting in continued infertility of PCOS patients. Those patients treated medically to ovulate are at higher risk for ovarian hyperstimulation syndrome, a potentially lethal condition.

5. Dermoid Cysts: A benign germ cell tumor within the ovary that may contain elements of all three germ cell layers. This tumor is also called mature teratoma. It is among the most common of ovarian neoplasms, representing 20-25% of all ovarian neoplasms and 33% of all benign tumors. They vary in size from millimeters to 25 cm in diameter. They require surgical excision.

6. Corpus Luteum Cysts: Less common than follicular cysts but clinically important. They are usually associated with normal endocrine function or prolonged secretion of progesterone. They can reach 3 to 10 cm in size, and can rupture to cause intraperitoneal bleeding.

7. Ectopic Pregnancy: Pregnancy that develops following implantation of the blastocyst anywhere other than the endometrium lining the uterine cavity. The vast majority of ectopic pregnancies occur in the fallopian tube although they can also occur in the ovary, abdominal peritoneal cavity and the cervix.

8. Cornual Pregnancy: Pregnancy developing in the interstitial portion of the fallopian tube with the myometrium of the uterus. Like the tubal ectopic pregnancy, this type of pregnancy must be removed before it ruptures and causes massive bleeding.

9. Adenomyosis: The growth of endometrial glands and stroma in the uterine myometrium at a depth of at least 2.5 mm from the basalis layer of the endometrium. This condition is frequently associated with dysmenorrhea (painful menstrual cramps). It is generally treated with hysterectomy.

10. Uterine AV Malformation: The presence of abnormal vasculature within the pelvis that results in abnormally heavy bleeding, usually requiring multiple transfusions. It has been treated with hysterectomy or radiographic embolization.

11. Endometriosis: The presence and growth of glands and stroma identical to the linig of the uterus in an ectopic location outside of the uterus. This condition is frequently associated with development of pelvic adhesions and pelvic pain. The patient frequently has dysmenorrhea or dyspareunia (pain with intercourse). Endometriomas are cysts within the ovary filled with endometriotic fluid that are also known as chocolate cysts because of their appearance.

12. Endometrial Hyperplasia: This condition is a variety of patterns of epithelial and stromal proliferation that have in common an abnormal increase in the cellular number within the endometrium. The cells can develop atypical features that can eventually develop into malignancy. This condition is frequently associated with

irregular bleeding in women. In women who are done with childbearing, hysterectomy or endometrial ablation is usually recommended.

13. Multifetal Pregnancy: With the advent of fertility drugs, women frequently achieve multiple pregnancy with twins, triplets, or even greater number of gestational sacs. Selective reduction of these sacs are performed regularly due to the increased risk to both the mother and the babies incurred by the multiple nature.

14. Excessive Bleeding which could be due to a number of OB/GYN problems.

Also a variety of possible applications of HIFU are shown in figures7 and 8.

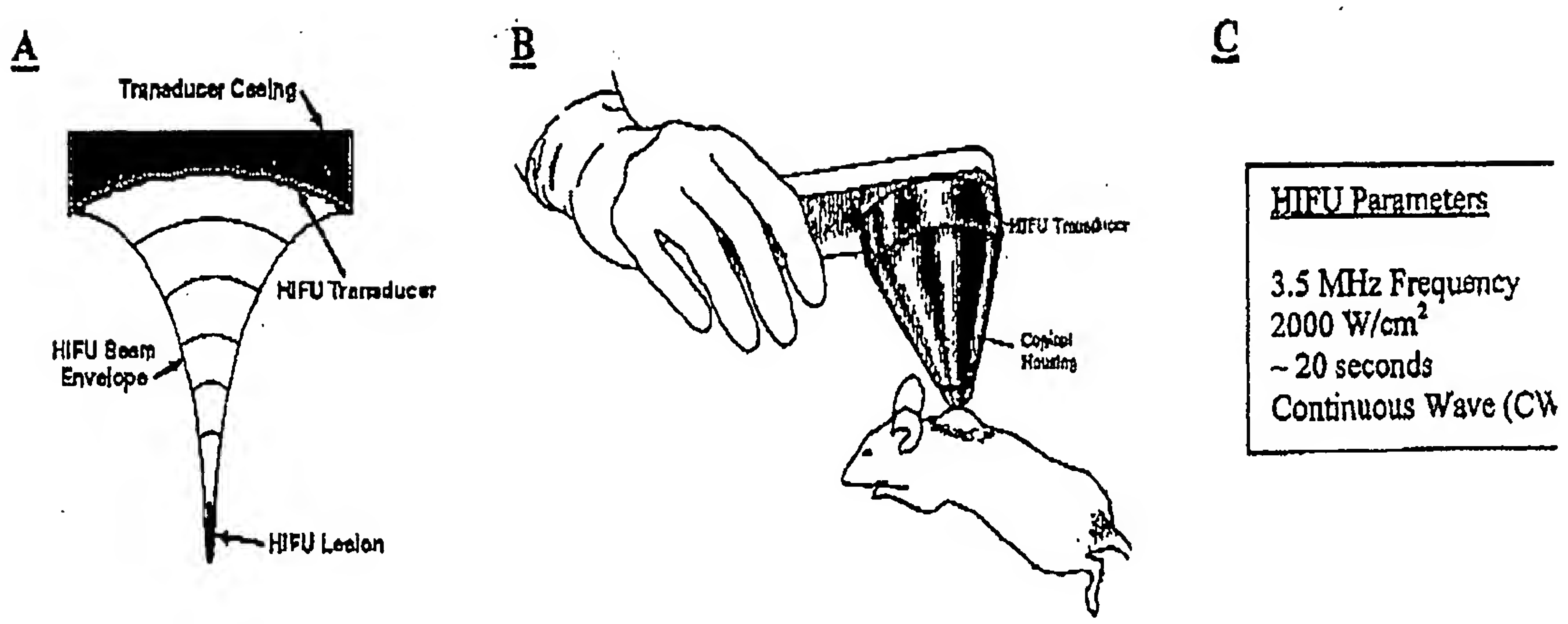


Figure 1. A. Schematic diagram of a HIFU transducer, and lesion formation. B. Schematic diagram of the method of treatment of tumors in nude mice. C. The HIFU parameters of the treatment.

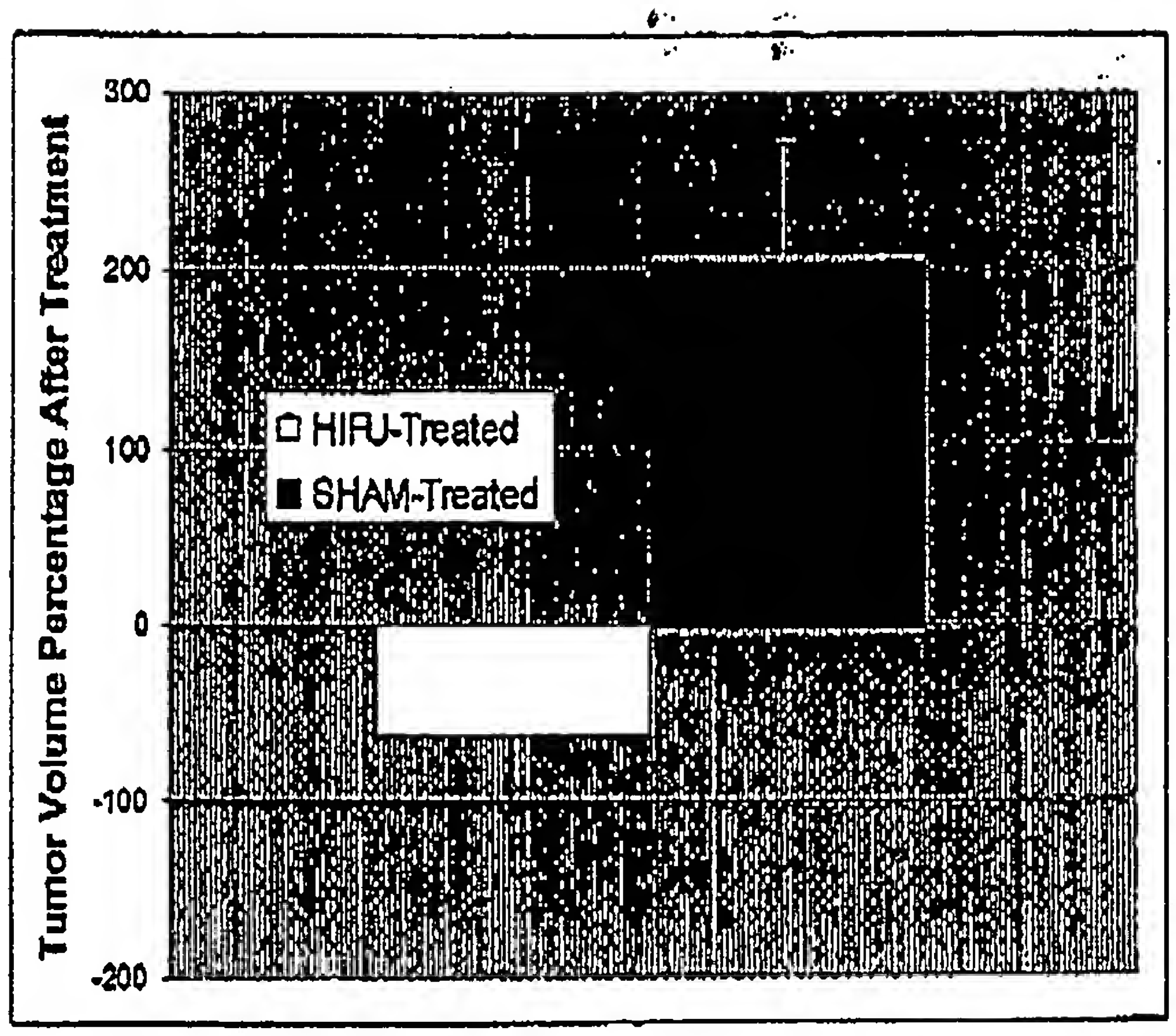


Figure 2. Average change in the tumor volume after treatment.

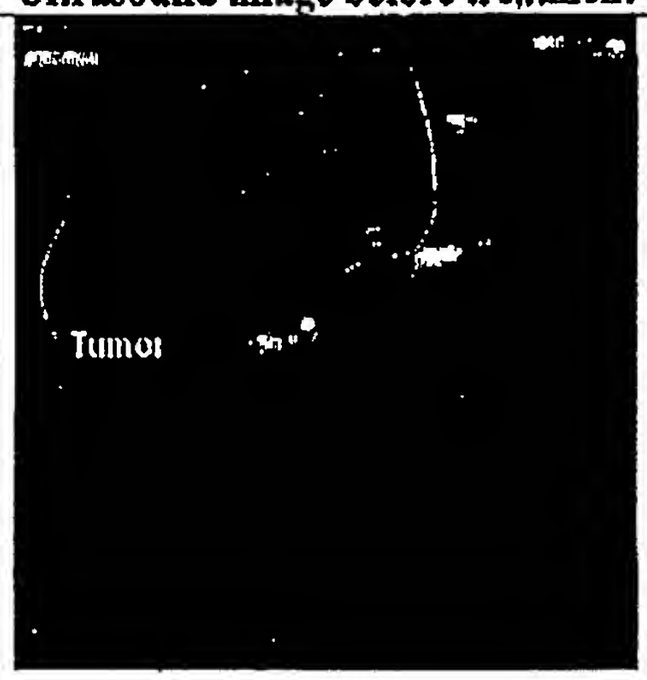
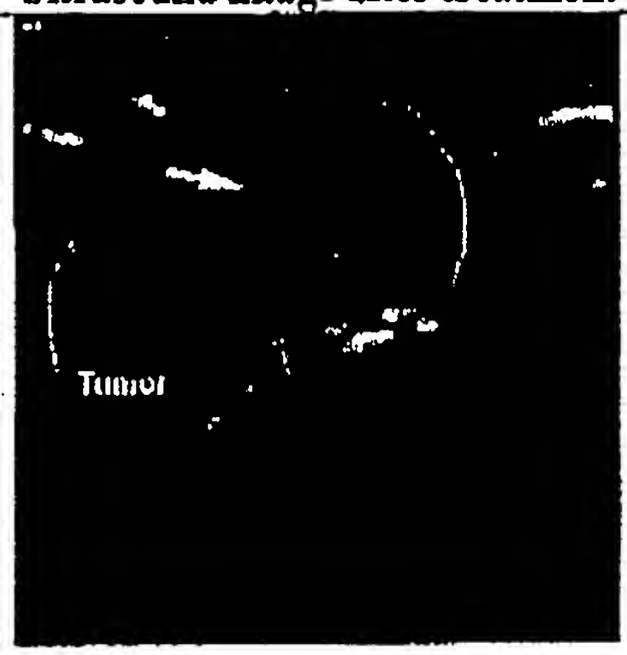
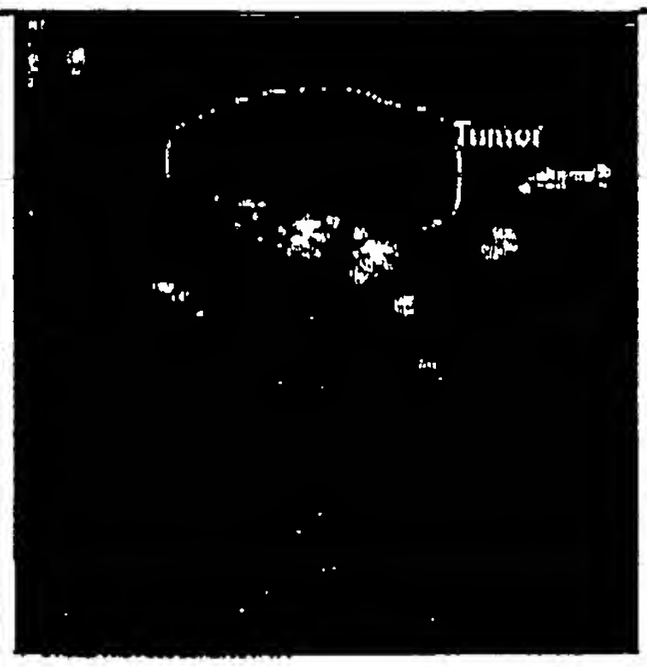
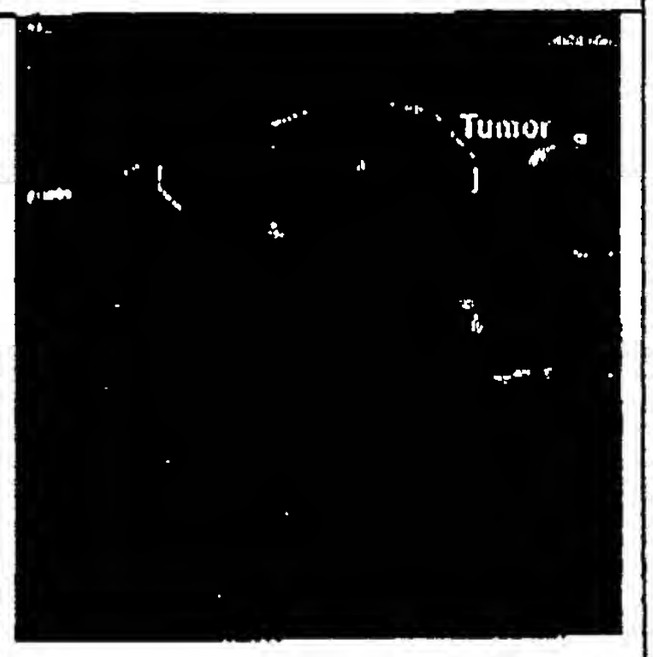
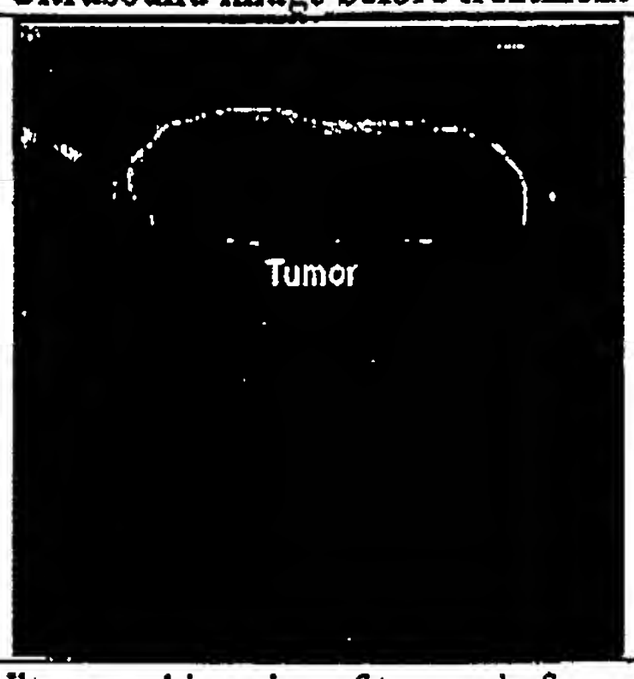
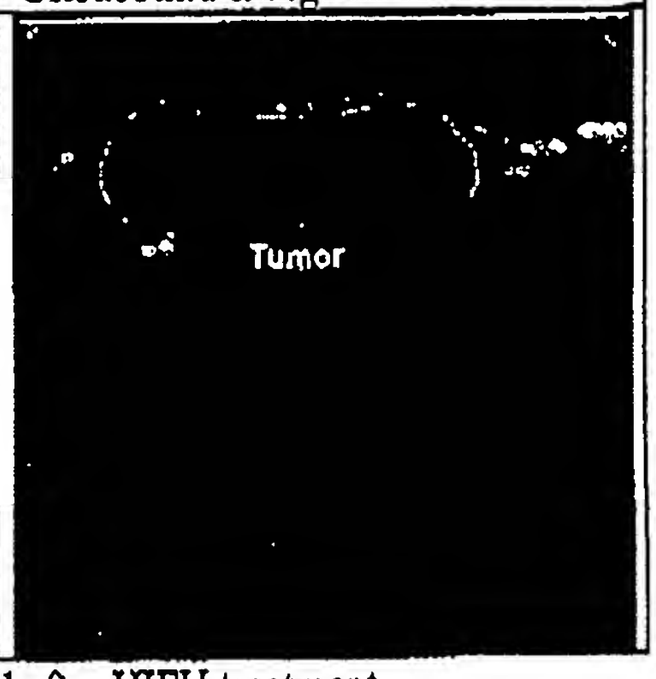
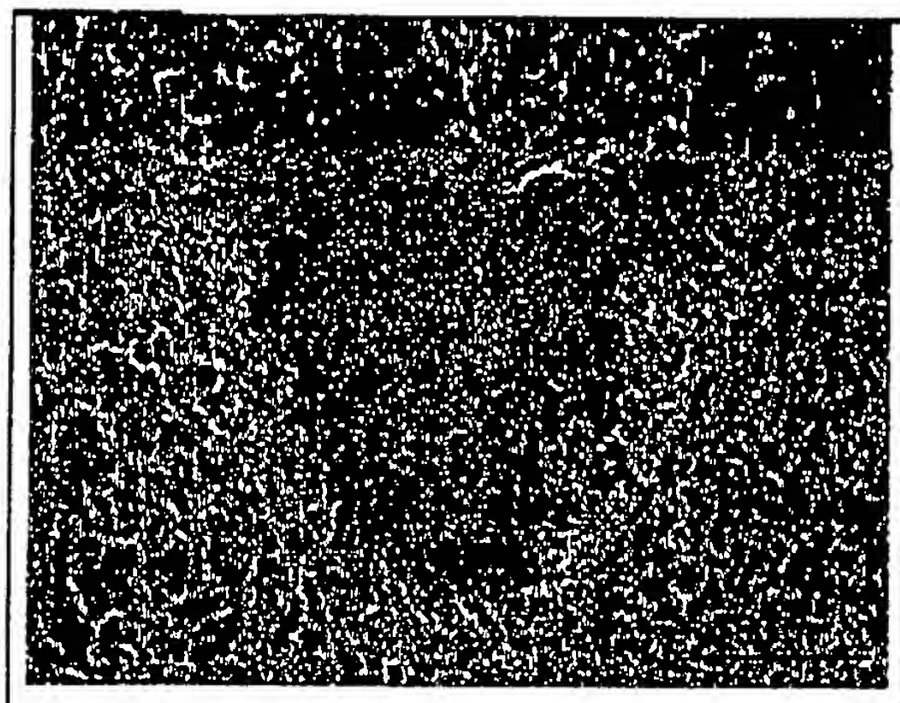
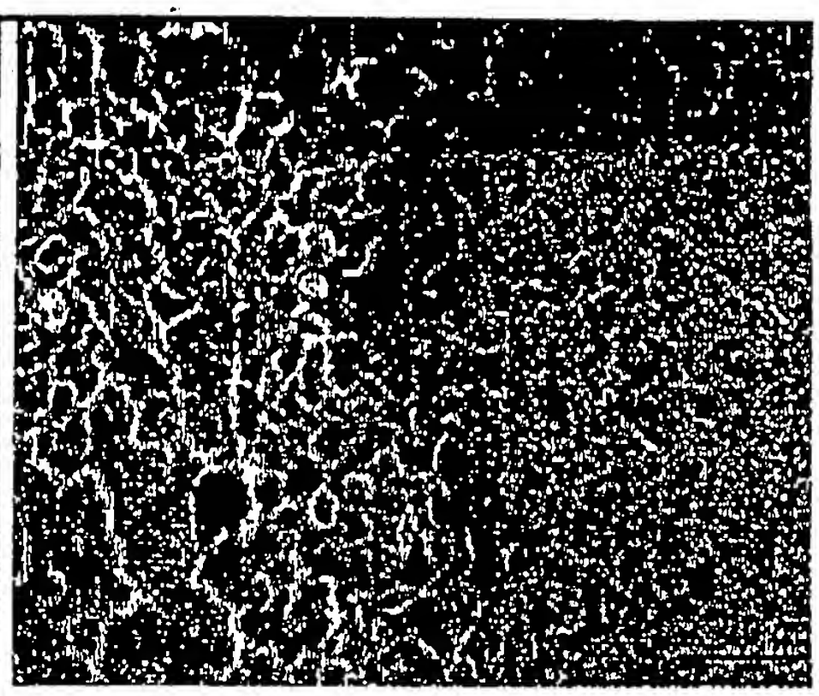
	Ultrasound image before treatment	Ultrasound image after treatment
Case 1 HIFU treatment of a lobulated tumor. The division line between the lobes is seen in the ultrasound image before treatment. The arrow on the image after the treatment shows possibly the HIFU lesion.		
Case 2 HIFU treatment of an tumor. The tumor became hyperechoic after HIFU treatment.		
	Ultrasound image before treatment	**Ultrasound image after treatment**
Case 3 SHAM treatment of a tumor. The appearance of the tumor did not change after the SHAM treatment.		

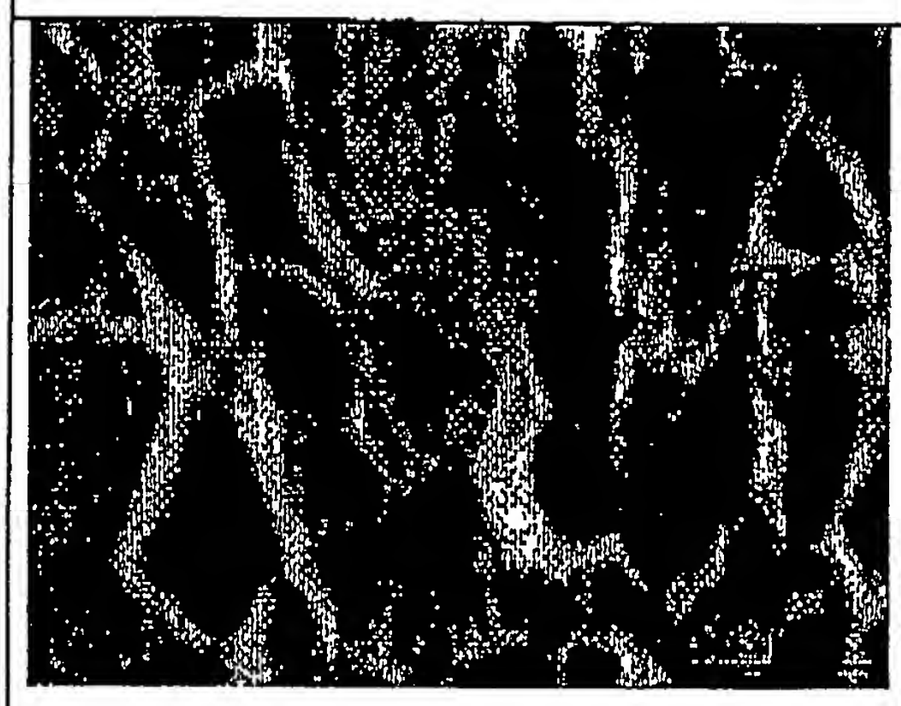
Figure 3. Ultrasound imaging of tumors before and after HIFU treatment.



Necrosis of the tumor cells represented as dark pink stained regions.



Sharp demarcation between the necrosed and normal tumor cells. The necrosed cells appear v pyknotic nuceli, indicating coagulation necrosis the HIFU-treated region.



Normal tumor cells, with intact nuclei. No sign of necrosis is observed.

Necrosed tumor cells with nuclear fragmentatio (arrows).

Figure 4. Histology of tumors.

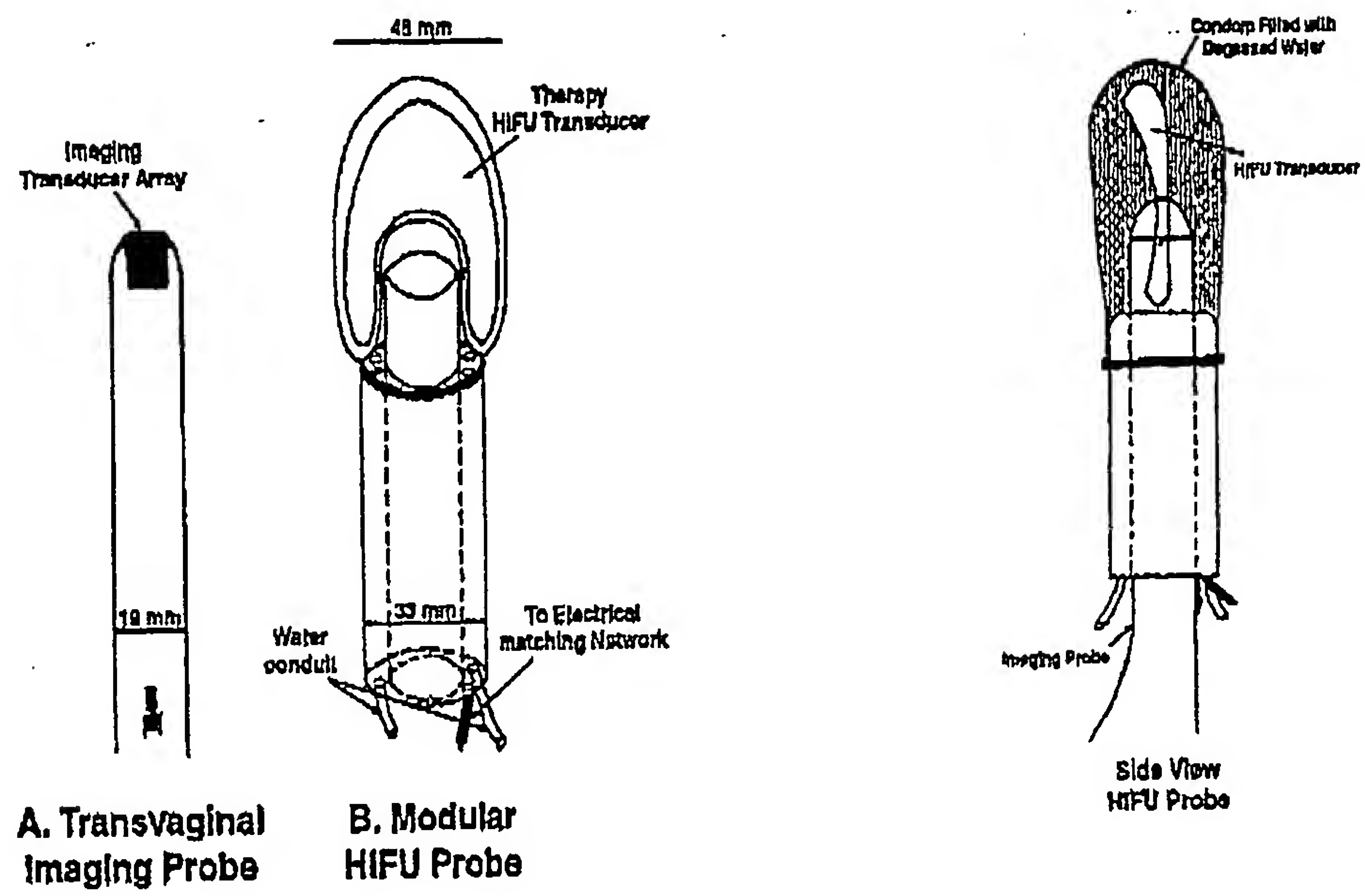


Figure 5. An embodiment of a transvaginal HIFU probe.

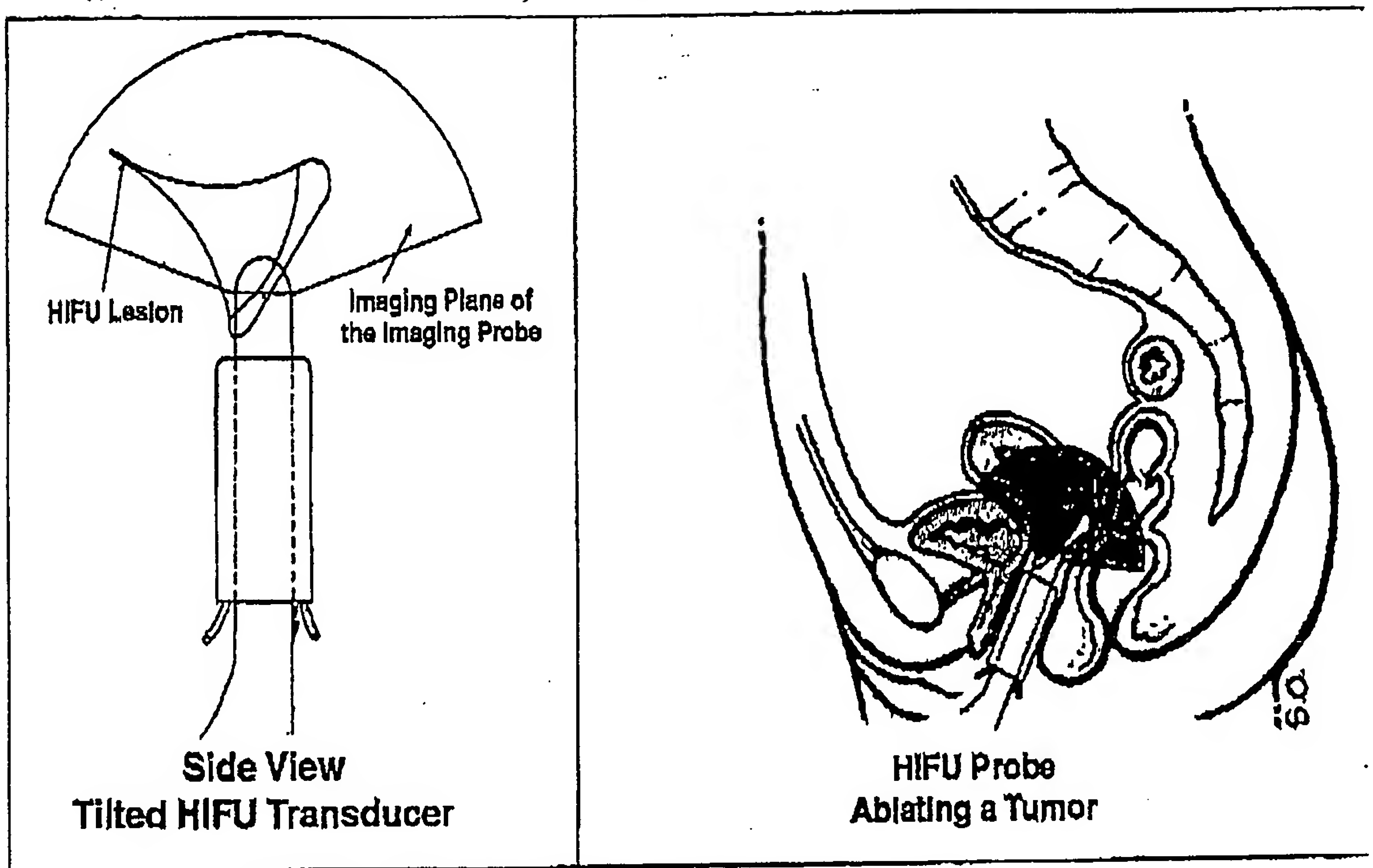


Figure 6. Probe placement and use for a uterine fibroid.

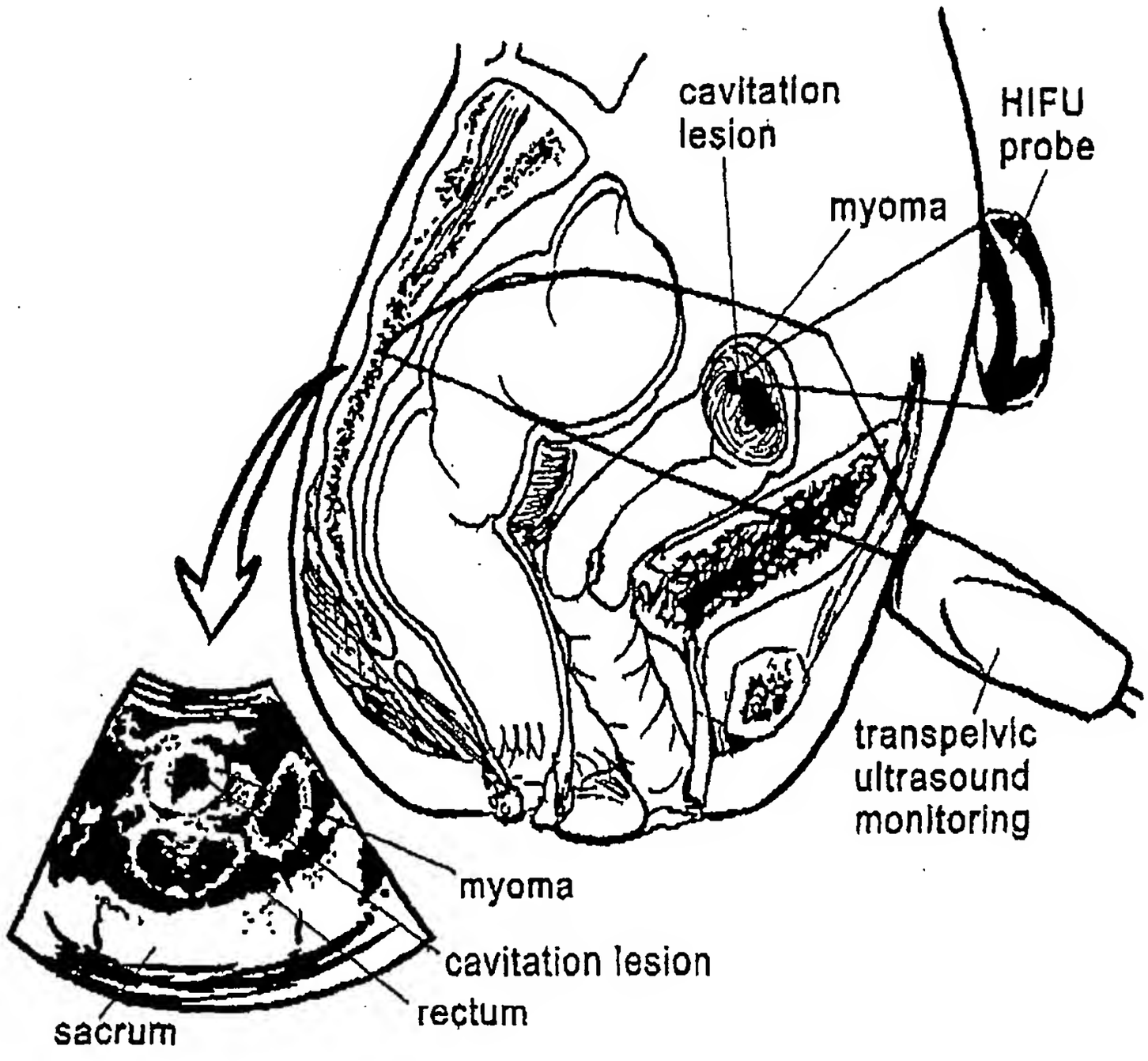


Figure 7. Trans-abdominal treatment and monitoring of a uterine fibroid.

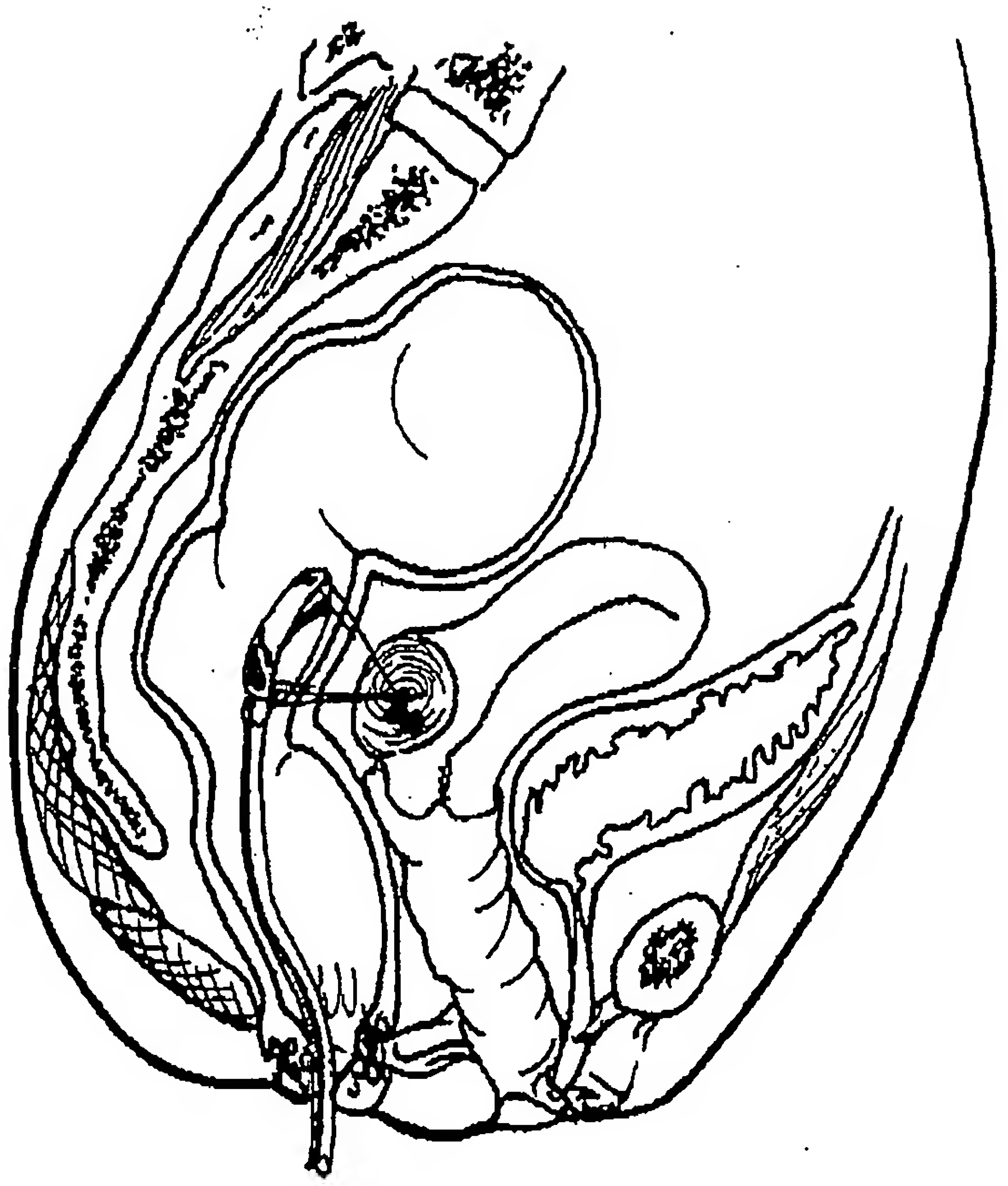


Figure 8. Transrectal treatment of a uterine fibroid.